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EXAMINER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/615,518	LEIDEN, JEFFREY M.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 4-11, 24, and 27-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-11,24,27-29 and 31-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed January 13, 2009 has been entered. Claims 1, 11, 24, 36, and 37 have been amended and Claims 2, 3, 25, 26 have been cancelled.

Accordingly, Claims 1, 4-11, 24, and 27-51 remain pending in the instant application.

The remarks filed on June 4, 2008 (hereinafter referred to as "the response") are considered herein.

Applicants elected the species "growth factor" in the response filed April 3, 2006. Although Claims 5 and 30 have been amended to remove the term "growth factor," the broad claims continue to read on the elected species.

Claims 5, 30, and 38-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 3, 2006.

Accordingly, Claims 1, 4, 6-11, 24, 27-29, and 31-37 are examined herein.

The rejection of Claims 1, 4, and 6-10 under 35 U.S.C. 102(b), as being anticipated by Tripathy et al. (1994, PNAS 91: 11557-11561, cited on IDS), is **withdrawn** in view of the amendment to Claim 1.

The rejection of Claims 24, 28, 29, 31, 32, 34, 35, and 36 under 35 U.S.C. 102(b), as being anticipated by Dhawan et al. (1991, Science 254: 1509-1512, cited on IDS), is **withdrawn** in view of the amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 6-11, 24, 27-29, and 31-37 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) a process for increasing the circulating levels of a self protein in the blood stream of an immunocompetent animal, wherein the method comprises delivering an adenoviral vector *in vivo* to muscle cells of said animal by intramuscular injection in an amount sufficient to obtain expression of and increase the circulating level of said self protein in the bloodstream of said animal for a period greater than about 30 days, wherein said self protein is erythropoietin or a growth hormone and undergoes secretion, diffusion or transport to the circulation upon expression *in vivo*; and

(ii) a process for increasing the circulating levels of a self protein in the blood stream of an immunocompetent animal, wherein the method comprises transforming muscle cells of said animal *ex vivo* with an adenoviral vector encoding a self protein to thereby produce transformed muscle cells, wherein said self protein is erythropoietin or a growth hormone and undergoes secretion, diffusion or transport to the circulation upon expression *in vivo*; and delivering said transformed muscle cells by intramuscular injection to said animal in an amount sufficient to obtain expression of and increase the circulating level of said self protein in the bloodstream of said animal for a period greater than about 30 days,

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims as amended are directed to a method for increasing the circulating levels of a hormone in the bloodstream of an immunocompetent human with a hormone deficiency, wherein the method comprises delivering a viral vector *in vivo* to muscle cells of said animal by intramuscular injection in an amount sufficient to obtain expression of and increase the circulating level of said hormone in the

bloodstream of said human for a period greater than about 30 days, wherein said hormone undergoes secretion, diffusion or transport to the circulation upon expression *in vivo*. The claims were amended during prosecution to remove the "self protein" limitation. Although the preamble has been amended to recite an intended use "for treating an immunocompetent human with a hormone deficiency," the claims do not require a treatment effect. Since a treatment effect is not required, the claim-designated effect of increasing the circulating level of said hormone in the bloodstream of said human for a period greater than about 30 days, wherein said hormone undergoes secretion, diffusion or transport to the circulation upon expression *in vivo* is the only effect required.

The specification fails to provide an enabling disclosure for the claimed methods over the full scope because the specification teaches that the only use for the methods are for gene therapy (p. 1, lines 20-22). No other use for the claimed methods are contemplated in the specification. However, the specification does not adequately teach how to use the methods in gene therapy applications. The specification fails to teach any method for transferring any gene into a target cell and expressing that gene at a therapeutic level in a diseased animal. Thus, the specification does not adequately teach how to use the claimed methods.

The claims encompass methods of gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must teach how to use the claimed methods with specific guidance. However, the specification does not provide any guidance as to the use of the claimed DNA methods to treat a diseased animal. The specification does not teach the level of gene expression required, the number of transduced cells needed, when or for how long the gene should be expressed, or the frequency of administration of the gene therapy vector required, for treatment of any pathological condition. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December

1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed methods for *in vivo* or *ex vivo* gene therapy. Thus, absent any showing that the claimed methods can be used in gene therapy applications to produce the intended therapeutic effect, the claims directed to methods for gene therapy are not enabled by the disclosure over the full scope.

The gene therapy art as a whole clearly demonstrates that even in the year 2001, despite intensive effort in every aspect of gene therapy, success in the field was quite limited. Furthermore, Rubanyi et al. (2001) was published after the effective filing date of this application and reflects essentially the same opinion as those stated in the other references cited regarding the technical barriers and very limited clinical efficacy. The quotes that Applicants refer to describing the optimism in the field of gene therapy is not indicative of enablement at present, but rather suggest that continued effort should result in successful protocols at some time in the future. However, future potential is not sufficient to demonstrate the need for only routine experimentation rather than undue experimentation, given that the art as a whole demonstrates that intensive effort has met with limited success.

The specification fails to provide an enabling disclosure for the method of increasing the circulating level of <u>any</u> gene product in the bloodstream of a primate, other than those listed above. The

guidance and examples provided in the specification are limited to producing elevated levels of erythropoietin (EPO) in the bloodstream of a healthy Cynomolgus monkey. Since methods of gene therapy are not routine for the reasons discussed above, undue experimentation would have been required to produce the desired effect using any other gene.

The specification provides examples demonstrating that serum erythropoietin levels and hematocrits are elevated in Cynomolgus monkeys following a single intramuscular injection of an erythropoietin-encoding adenovirus vector (Example 8). An assessment of the safety of the administered adenovirus vector is also described (Example 9). However, none of the examples are directed to applications that result in treatment of a pathological condition in a primate. Moreover, the specification does not offer any guidance in this regard.

Given the limited working examples, the limited guidance in the specification, the broad scope of the claims, and the unpredictability of using the claimed methods in gene therapy applications, undue experimentation would have been required for one skilled in the art to practice the claimed invention.

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts have held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

At page 9, paragraph 2 of the response, Applicants go on to assert that the specification provides substantial and detailed information regarding the claimed processes of treating a hormone deficiency. Applicants point to the specification for teaching proteins present in the circulation of an animal, viral vectors that can be used in the invention, *in vivo* and *ex vivo* transformation of muscle cells, and processes for increasing the circulating levels of a self protein in the bloodstream of an immunocompetent animal

by delivery of viral vectors to muscle cells *in vivo*, in Examples 5-10. Applicants further assert that the plasmid vectors taught in Examples 1-4 can be applied by one of ordinary skill in the art in the practice of the claimed methods. As regards the working examples, Applicants assert that the data set forth in the specification demonstrates that the processes claimed result in stable long-term expression of a self protein in an immunocompetent subject. However, the data that Applicants refer to pertain only to expression of erythropoietin, and therefore the specific guidance of the specification is extremely limited. Applicants are reminded that a scope of enablement has already been acknowledged for the methods set forth in the examples. The rejection is directed to everything outside the acknowledged scope of enablement. As regards the very broad scope of serum proteins and possible vectors that may be used in the claimed methods, the guidance set forth in the specification is in the form of general guidance, rather than the specific guidance that is needed in an art as unpredictable as gene therapy. The only specific guidance provided is for increasing the circulating level of erythropoietin, which has already been acknowledged as enabled.

At page 10 of the response, Applicants dispute the argument that the specification does not provide guidance as to how the claimed processes can be used in the treatment of disease in an animal. In response, Applicants note that "the results set forth in the specification can be safely and effectively applied to treat patients with Epo-responsive anemias." Applicants seem to be addressing a rejection that has not been made. Applicants are reminded that the Examiner has already acknowledged that the specification is enabling for increasing the circulating levels of erythropoietin. The rejection is directed to the remaining scope of the claim. Accordingly, this argument does not pertain to the rejection. As noted in the rejection of record, the guidance and examples provided in the specification are limited to producing elevated levels of erythropoietin (EPO) in the bloodstream of a healthy Cynomolgus monkey. Since methods of gene therapy are not routine for the reasons discussed above, undue experimentation would have been required to produce the desired effect using any other gene. Thus, the argument that the

guidance of the specification would enable one of skill in the art to treat patients with Epo-responsive anemias does not address the rejection of record.

At page 11, paragraph 1 of the response, Applicants contend that they are not required to explicitly recite every disease that can be treated using the processes of the invention. The rejection of record does not pertain to a recitation of the diseases that can be treated using the method of the invention. It is acknowledged that the claims cover the treatment of a vast number of widely divergent diseases that may be treated by increasing the circulating level of a vast number of widely divergent serum proteins. Given the huge number of widely divergent diseases that may be treated by expressing any of a vast number of widely divergent serum proteins in the bloodstream using any of a very large number of possible expression vectors in any species of animal, the specification must enable the treatment of a wide variety of diseases by the claimed methods. Here, it enables only the treatment of Epo-responsive anemias.

At page 11, paragraph 2 of the response, Applicants assert that the burden of setting forth a *prima facie* case of unpatentability under 35 U.S.C. 112, first paragraph is with the Examiner and that no reasonable basis has been set forth to establish that one of ordinary skill in the art would not be able to apply the information set forth in the specification to increasing the circulating level of other hormones, and applying the claimed methods to the treatment of diseases. On the contrary, ample reasons have been provided to demonstrate the unpredictability in the art and the limited guidance in the specification. The unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman,* 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). The unpredictability in the art of gene therapy has been amply established by the rejection of record. While the PTO bears the initial burden of

providing reasons for doubting the objective truth of the statements made by Applicants as to the scope of enablement, when the PTO meets this burden, the burden shifts to applicant to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

At page 11, paragraph 3 of the response, Applicants assert that specific guidance pertaining to the level of gene expression required in the context of erythropoietin is provided in the specification at pages 6-8. Applicants note that this section provides detailed information regarding dosage of viral vector and effect of dose modification on serum erythropoietin level and hematocrit. Applicants are again reminded that the Examiner has already acknowledged that the specification is enabling for increasing the circulating levels of erythropoietin. As noted above, the rejection of record is directed to the remaining scope of the claim and therefore this assertion does not address the rejection of record.

At page 12, paragraph 2 of the response, Applicants assert that the claims are directed to methods for increasing the circulating level of a hormone in the bloodstream of an immunocompetent animal and that "[i]f expression of such gene is no increased, then the process or method falls outside the scope of the claimed invention." However, the claims cover both therapeutic and non-therapeutic increases in the circulating level of a hormone and methods for obtaining expression of a protein at non-therapeutic levels is relatively routine in the art of gene transfer. In contrast, methods for obtaining expression of a protein at therapeutic levels is not routine in the art of gene therapy, for reasons of record. Nevertheless, the claims cover therapeutic protocols and the specification fails to enable the full scope of therapeutic protocols, for reasons of record. Moreover, the only use for the claimed invention is for therapy. Applicants further allege that determining a response to therapy and determining how much of an expression of a gene may be sufficient to result in a therapeutic response falls within the level of ordinary skill of one of ordinary skill in the art. On the contrary, given the huge number of widely divergent diseases that may be treated by expressing any of a vast number of widely divergent serum proteins in the

bloodstream using any of a very large number of possible expression vectors in any species of animal, in combination with the unpredictability in the art, the skilled artisan would not be able to predict which protocols would be successful, among the many possible protocols that could be attempted. Given the very broad scope of the claims, the specification must enable the treatment of a wide variety of diseases by the claimed methods. Here, it enables only the treatment of Epo-responsive anemias.

At page 12, paragraph 2 of the response, Applicants allege that each of the issues set forth by the Examiner, including when and for how long a gene should be expressed, are questions which are readily addressed by those of ordinary skill in the art and further that while some assessment may be required to optimize the method to result in a therapeutic effect, no reasonable basis has been set forth by the Examiner to establish that any undue experimentation would be required to optimize dose to result in a therapeutic response. As the cited art of record shows, those of very high skill in the art have applied **intensive investigation** trying to develop therapeutic protocols from the launching point of non-therapeutic protocols with extremely minimal success despite innovative approaches. This is not a matter of optimization. If it were only a matter of optimizing dose or altering certain parameters in accordance with clear guidelines as to which direction to proceed, then many therapeutic protocols would already exist, given the very high degree of motivation in the field to develop therapeutic gene therapy protocols. Again, this is not a matter of optimization.

At page 13 of the response, Applicants cite Svensson et al. (April 1996) for stating that there has been tremendous growth in the field of gene therapy, for providing an overview of the state of the art regarding muscle-based gene therapy, and for suggesting diseases that could be targeted using gene-based therapy. It is unclear how this contributes to the enablement of the claimed invention, particularly given that the reference seems to disclose no more than the present specification. Growth in the field of gene therapy does not indicate widespread success in the field, but only indicates that **intensive effort** has been applied to the development of gene therapy protocols with minimal success. It does not in any way

suggest that a single successful protocol could be readily modified by one of ordinary skill in the art using nothing more than routine experimentation to treat other disparate diseases with different etiologies and different pathological processes.

At pages 13-14 of the response, Applicants assert that the quotes the Examiner refers to in describing pessimism in the field of gene therapy are "not indicative of enablement in the state of the art pertaining to muscle-based gene therapy" and that the quotes merely suggest that continued effort should continue to improve gene therapy technology. Applicants further assert that the instant specification shows that methods of the present invention have found application in the treatment of disease and that the examples can be applied in providing guidance to one of skill in the art to increase serum levels of a protein to treat disease. Applicants further state that, while some experimentation may be required to practice the claimed invention, no sufficient evidence has been set forth by the Examiner to show that any such experimentation would be undue experimentation. On the contrary, ample reasons supporting unpredictability in the field of gene therapy and the need for undue experimentation to enable the full scope of the claims have been provided. The claims cover the treatment of a vast number of widely divergent diseases that may be treated by increasing the circulating level of a vast number of widely divergent serum proteins. Given the huge number of widely divergent diseases that may be treated by expressing any of a vast number of widely divergent serum proteins in the bloodstream using any of a very large number of possible expression vectors in any species of animal, the specification must enable the treatment of a wide variety of diseases by the claimed methods. The claims cover the treatment of disparate diseases with different etiologies and different pathological processes. Applicant's arguments are not commensurate in scope with the scope of the claims, do not adequately rebut the unpredictability in the field of gene therapy, and do not provide any evidence that the entire scope of the claim can be practiced using nothing more than routine experimentation in an art as unpredictable as gene therapy. As the art of record shows, methods for achieving expression of genes at non-therapeutic levels are relatively

routine, but gene expression is not gene therapy. The development of therapeutic protocols in gene therapy is highly unpredictable and must be done on a case-by-case basis. The considerable research effort in the field of gene therapy has been necessitated by the inherent problem of the myriad of parameters that may be adjusted and combined in a myriad of ways to develop therapeutic protocols and the consideration of numerous disease-specific factors that evolve as the research effort progresses. The skilled artisan would not be able to predict which protocols would be successful, among the many possible protocols that could be attempted. Lacking predictability, considerable experimentation is required. Applicant's focus on optimism in the field of muscle-based gene therapy is missplaced because a potential for the future of gene therapy does not constitute enablement at the time of the invention, but rather is suggestive of a technology that is still undeveloped, despite considerable effort in the field. One of skill in the art would conclude that the development of gene therapy protocols is not routine if potential successes lie predominantly in the future, not in the past. The references cited in Applicant's response and by the Examiner provide clear evidence that **intensive effort** has been applied to the development of gene therapy protocols with minimal success. None of the gene therapy methods that Applicants point to were developed using routine experimentation. Furthermore, if it was a simple matter to take the vectors used by others and, with routine experimentation, manipulate them and apply them in techniques for the treatment of other diseases, many successful gene therapy protocols would already exist. However, this is not the case, as evidenced by the references cited in the rejection of record. Further **research** is required to accomplish these goals, not routine experimentation. Thus, the references cited by Applicants do not constitute evidence that only routine experimentation is required for the development of gene therapy protocols within the scope of the claims. On the contrary, the references clearly indicate that, in each instance, **intensive investigation** was required to develop experimental protocols. In an unpredictable art, considerable specific guidance is needed from the specification. In the instant case, given the limited guidance in the specification with regard to the design and implementation of vectors for *in vivo* and *ex*

vivo muscle-based gene therapy, the limited applicable working examples directed to administering an Epo-encoding viral vector, and the broad scope of the claims with regard to the disparate diseases covered, the vast number of vectors that could be used, and the widely divergent serum proteins to be expressed, undue experimentation would have been required for one skilled in the art to practice the claimed methods over the full scope at the time of the invention.

At page 15 of the response, Applicants cite Wang and Herzog (2005) as evidence that the claimed methods can be used in gene therapy applications to produce a therapeutic effect. However, given that the priority date of the instant application is August 1996, this reference is post-filing art and evidences that considerable undue experimentation was involved in developing a therapeutic protocol for the treatment of hemophilia. The abstract notes the "recent innovative approaches in vector design and delivery, and strategies to circumvent immunological limitations" and concludes that "these studies provide much encouragement for the possibility of future clinical success, but also point out hurdles that still have to be overcome." This is 9 years after the effective filing date of the present application. The reference also notes that "gene therapy for hemophilia has been extensively pursued over the past decade" (page 349, column 1, paragraph 2). The reference reveals that in earlier studies "only sustained expression of sub-therapeutic or transient expression of therapeutic levels had been reported" (page 349, column 2, paragraph 2). The present claims require sustained expression for 30, 60, 90, 120, and 365 days. Thus, the limited success reported in 2005 was preceded by numerous failures, further experimentation, and intensive effort to come up with the "recent innovative approaches in vector design and delivery" referred to in the abstract, which only further evidences the unpredictability in the art. Furthermore, the reference aptly demonstrates that consideration of factors that were not appreciated at the time of the instant invention were crucial in developing the improved method described therein, further demonstrating the intensive effort applied to the development of the protocol. Citing numerous references from 1999, 2001, and 2004, the authors note that "animals with gene deletions or nonsense

mutations have a greater risk of inhibitor formation in muscle gene transfer than those with missense mutations" (page 352, column 2, paragraph 1). All subsequent clinical trials for Factor IX gene therapy for hemophilia were limited to subjects having missense mutations. The reference goes on to describe "[a] number of innovative approaches … under taken in order to improve efficacy and safety of muscle-directed F.IX gene transfer" (page 352, column 1, paragraph 3). Citing a 2005 report, the reference further emphasizes that "[i]n addition to improvements in vector design, delivery techniques may hold the key for optimal therapy. A substantial increase in efficacy of muscle-directed AAV-F.IX delivery has recently been documented for local vascular delivery" (page 353, column 1, paragraph 2). Thus, the reference evidences considerable intensive effort, innovation, and undue experimentation in developing the gene therapy protocol described. Given that Wang and Herzog (2005) is post-filing art, the skilled artisan would not have had the benefit of the teachings contained therein at the time of the instant invention in 1996.

At page 15 of the response, Applicants cite Kay et al. (2000) and Manno et al. (2003) as evidence that the claimed methods can be used in gene therapy applications to produce a therapeutic effect. Again, both references are post-filing art and there is no evidence that the protocols described therein were the result of routine experimentation. Furthermore, the present specification provides no guidance at all with regard to Factor IX gene therapy. As discussed above, consideration of factors that were not appreciated at the time of the instant invention were crucial in developing the limited methods described therein, further demonstrating the intensive effort applied to the development of the protocol. The references evidence further developments in vector design, further experimentation, and strategies for limiting immune responses by selection of specific patient populations, all of which indicate undue experimentation rather than routine experimentation. Since the references are post-filing art, the skilled artisan would not have had the benefit of the teachings contained therein at the time of the instant invention in 1996.

At pages 15-16 of the response, Applicants allege that the references are not cited to show the state of the art at the time the present application was filed, but are cited to demonstrate that the present specification as written is enabling for the scope of the claims, and to demonstrate that the claimed method can in fact be used in gene therapy application. It cannot be said that the specification as written is enabling for the entire scope of the claims when the present specification provides no guidance at all with regard to Factor IX gene therapy and the references themselves evidence the exercise of undue experimentation in arriving at the protocols disclosed therein. Furthermore, it cannot be said that the specification enables the entire scope of the claims when the skilled artisan would not be able to predict which protocols would be successful, among the many possible protocols that could be attempted. Furthermore, it cannot be said that the specification as written is enabling for the entire scope of the claims when the teachings of the specification are limited to providing vector-mediated expression of a self protein, whereas the instant claims have been amended to encompass expression of non-self proteins, for which the specification provides no guidance whatsoever. There is no guidance at all for achieving therapeutic levels of non-self proteins and the specification explicitly teaches away from the use of non-self proteins.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action

is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632